THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 17

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte A. SAID EL SHAMI,
CHRISTOPHER W. HAND,
SUSAN A. MILLER
and ROBERT A. MOORE

Appeal No. 93-3369
Application 07/344,179[1]

ON BRIEF

Before SCHAFER, Vice-Chief Administrative Patent Judge, and GRON and WEIMAR, Administrative Patent Judges.

WEIMAR, Administrative Patent Judge.

DECISION ON APPEAL

This appeal is from the Final Rejection of claims 70-90.

Claim 70 is illustrative of the subject matter on appeal and reads as follows:

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[1] Application for patent filed April 26, 1989.

70. A diagnostic device for measuring analytes in samples of biological fluids which comprises:

a column-type assembly defining a fluid pathway having an open end adapted to receive a sample of biological fluid to be analyzed, said fluid pathway being bridged by a first solid phase support, and an effluent discharge point on the side of said support opposite said open end,

a sleeve-type container having an open end and a closed end, said column type assembly being received in said open end of said sleeve-type container,

a specific antibody binder covalently immobilized on said first solid phase support to which an analyte label is pre-reacted to saturate substantially all binding sites on said binder to form a first solid phase specific antibody binder-analyte label complex, said solid phase complex when contacted with a biological fluid sample containing a specific analyte, being adapted to have displaced therefrom labeled analyte in an amount directly proportional to the concentration of the specific analyte,

a second solid support, spaced apart from first solid phase support, housed at the closed end of said sleeve-type container and in proximity to said effluent discharge point, said second solid support when contacted by the displaced labeled analyte from the effluent discharge point of said first solid phase complex, being adapted to produce a visible color on said second solid support either directly or after the addition to said second solid support a substance capable of reacting with the analyte label to produce a visible color.

The references relied upon by the examiner are:

Graas	4,270,921	June 2, 1981
Liotta	4,446,232	May 1, 1984
Diamond et al. (Diamond)	4,766,062	Aug. 23, 1988
Diekmann	4,956,298	Sep. 11, 1990

Claims 70-90 are rejected under 35 U.S.C. § 103 over Diamond in combination with Liotta.

Claims 70-90 are rejected under 35 U.S.C. § 103 over Diekmann in combination with Liotta.

Claims 70-90 are rejected under 35 U.S.C. § 103 over Graas in combination with Liotta.

Background

Various diagnostic devices for determining the presence or absence of a particular molecule of interest in a sample had been developed prior to the filing date of this invention. These devices had been used to detect various molecules of interest, including drug residues and specific hormones in urine samples and in blood samples. The detection materials associated with diagnostic devices, their specific design and their mode of action varied as well.

The use of immobilized materials which specifically bind to a particular molecule of interest, and thus separate it from a sample, was known in the art prior to the filing date of this application. Also known, were techniques for labeling immobilized materials involved in the specific binding required for

separation of a molecule of interest. The labeling allowed for identification of a positive result, i.e., the molecule of interest was present in a sample. See the specification at pages 1-8.

Devices known in the prior art range in design from paper test strips to packed columns. Many of these devices are designed to separate a reaction region from a test display region. This is particularly true for devices that involve radioactive and colorimetric chemical labels.

The claimed diagnostic device at issue in this application is limited as to its structural features, that is a column with an effluent discharge point which fits into a sleeve, each of which column and sleeve contains a solid phase support, e.g. microparticles. The claimed device is also limited to antibody/analyte test materials contained in the solid phase supports. The two microparticulate supports of the claimed device provide a separate reaction region, i.e. the column, and a test display region, i.e. the bottom of the sleeve. See Figure 1 of the application. The issue is whether the particular claimed device would have been obvious to a person of ordinary skill in the art at the time of the invention.

The column-associated particulate support (hereinafter the column support) contains materials critical to the binding of a molecule of interest such that it can be separated from a sample added to the device. The sleeve-associated particulate support (hereinafter the sleeve support) contains material critical to detection of the binding should it take place in the support contained in the column.

All of the claims are limited to the use of antibodies and labeled analytes on the column support. The antibody is immobilized on this column support. The molecule of interest that the device is designed to detect is referred to throughout the claims as the "analyte." The term "analyte label" in the claims refers to a material that has been bound to the immobilized antibody on the column support, in which the analyte, or an analog thereof, is chemically labeled with a material which itself has a visible color or which can be reacted with other compounds to produce a compound which has a visible color. The amount of "analyte label" on the column support is high enough to saturate
substantially all of the binding sites of the antibody immobilized on the support.

In use the device functions in the following manner. A sample is added to the column. If there is any analyte in the sample it will displace the "analyte label" from the immobilized antibody when the sample contacts the column support. The analyte from the sample will remain bound to the immobilized antibody on the column support and the displaced "analyte label" will move through the discharge point of the column, into the sleeve and onto the sleeve support. This sleeve support is designed to absorb the "analyte label" and show its visible color or absorb it and an added compound which will react with the label to produce a visible color. See the paragraph bridging pages 12 and 13 of the specification.

Claim 70 from which all the claims ultimately depend sets forth functional language to limit the claim to materials which will result in "analyte label" displacement. When read in light of the specification, this functional language corresponds to the use of materials as an "analyte label" which will bind to the immobilized antibody with an affinity which is lower than the affinity of the analyte in a sample for the same immobilized antibody. The specification provides several examples of measuring the differences in affinity for the antibody and selecting an "analyte label" with an affinity such that it will

be displaced from the antibody by analyte in a sample but will remain bound to the antibody in the absence of analyte in the sample. Pages 14-17 of the specification set forth reaction and affinity constant equations that are required for selecting an "analyte label" molecule such that displacement of "analyte label" by any analyte that is in a sample will occur. See the examples of "analyte label" selection on pages 19-33 of the specification.

Discussion

The Examiner presents three rejections under 35 U.S.C. § 103, each of which involves the teachings of Liotta. The three references, Diamond, Diekmann and Graas, are each used in combination with Liotta, each one being set forth in a separate rejection. Liotta teaches a test strip and its use in antibody/antigen screening assays. The test strip contains a reaction zone and a display zone for indicating the presence of a labeled molecule.

The first rejection is premised on the following: Diamond teaches a DNA hybridization assay involving DNA probe materials that have been immobilized on a solid support with a labeled polynucleotide bound to the DNA probe material. The labeled polynucleotide is removed upon hybridization between the DNA

probe material and any DNA contained in a sample. The positive result of hybridization between the probe and sample DNA is indicated via detection of the removed labeled polynucleotide. The Examiner analogizes the competitive binding which causes the labeled polynucleotide displacement in Diamond to the competitive binding which causes the "analyte label" displacement in the claims at issue.

The Examiner refers to Example 14 of Diamond, at columns 33 and 34, which describes a process which includes binding the probe-labeled polynucleotide complex to agarose beads, which are placed in a disposable column; introducing the DNA-containing sample to the beads; incubating for two hours; transferring the beads into a small tube; centrifuging the material and recovering the eluate into a microfuge tube.[2] The Examiner then states at page 4, lines 7-14 of the Examiner's Answer that

> The beads in the column constitute a "column-type assembly" and first solid phase support as claimed; the microfuge tube constitutes a "sleeve-type container" and second solid support (the interior of the tube, as will be explained below) as claimed in claim 70. Although not explicitly stated, one of ordinary skill would have found it obvious to insert the discharge end

[2] We note that it is not apparent from reading Diamond that either the disposable column or the small tube have a discharge end, at least not one where the discharge end is opposite an open end, as required by the claims herein.

of the column in the microfuge tube opening in order to collect the eluate.

Diamond does not teach the use of antibodies and analytes and does not use a second solid phase support to absorb the removed labeled polynucleotide. Liotta is relied upon to supply these elements. The device of Liotta involves antibodies and analytes. In Liotta the analytes are referred to as antigens. The layered device of Liotta has two reaction zones on the same solid support, the latter of which provides means for detecting a labeled antibody or labeled antigen via a visible color.

The Examiner concludes that it would have been obvious to a person having ordinary skill in the art at the time of the invention to substitute the bound antibody-labeled antigen complex of Liotta for the polynucleotide complex of Diamond in the bead-packed column of Diamond, because the separations involved are analogous, and to provide a second solid support. For a more detailed discussion, we make reference to pages 4 and 5 of the Examiner's Answer.

The two additional rejections are similar in that both Diekmann and Graas disclose devices designed for use in centrifugation which are of a column and sleeve type assembly, with a reaction taking place on a solid support in the column. Each of these references provides a generic reference to use in

diagnostic assays. See the paragraph bridging columns 2 and 3 of Diekmann and in Graas, see column 4, lines 43-59 and column 9, lines 32-46. Neither Diekmann nor Graas teach the use of a solid support in the sleeve component of their devices. The rejection combines these teachings with those of Liotta in a manner similar to the above rejection to find the claimed column and sleeve type diagnostic device to have been obvious.

We do not agree that the claimed device is unpatentable in view of the combined teachings of any one of Diamond, Diekmann or Graas and the Liotta reference. The critical structural features of the claimed device are neither taught nor suggested by these references.

The claims at issue are drawn to a device not a method of using a device in a separation or diagnostic method. The analysis must focus on the elements of the claimed device. An argument centered on the extent of similarity between the mechanism of competitive binding displacement in Liotta's antibody/antigen diagnostic system versus chain migration displacement in Diamond's DNA hybridization assay is tangential at best to the issue of the obviousness of the claimed **device** over prior art **devices**.

The analysis of obviousness has been established since the decision in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966). This analysis requires acknowledgment of the differences between the prior art and the claims at issue. The differences from the prior art in this instance begin with the requirement in the claims of a column and sleeve type assembly each of which column and sleeve contains a solid phase support, with the column fitting into the sleeve such that the column discharge point is in proximity to the solid support in the sleeve. None of the references provide all of these elements. Substantially modifying the devices of the references is not suggested by the references themselves, nor have sufficient reasons been presented to explain why one of ordinary skill in the art would have made such changes to the prior art devices.

With regard to the lack of a teaching of a solid support in the sleeve, the Examiner states that the interior of the various tubes referred to in Diamond, Diekmann and Graas is analogous to a solid phase support in a sleeve, because one can detect visible color in both. The capacity to detect visible color inside a tube does not constitute a reason why one would modify a tube by inserting a solid phase support into the tube. The mere fact that they can operate to give a similar result does not establish

that one of ordinary skill in the art would consider them obvious alternatives for the devices taught by the prior art. Diamond makes no mention of a solid support for detection of the labeled polynucleotide either inside the microfuge collection tube or outside of the microfuge tube. With regard to Diekmann and Graas, not only do they not mention a solid support in the sleeve, their centrifugation sleeve tubes seem to be a particularly unlikely place for the addition of a solid support.

The rejections rely on Liotta to further provide the teaching of a second solid phase support for the sleeve of a diagnostic apparatus. Liotta teaches a dry, layered test strip and its advantages. See the paragraph bridging columns 1 and 2 of Liotta. The Examiner has failed to present any reason why one of ordinary skill in the art would separate the juxtaposed layers of Liotta's test strip into separate microfuge tubes or separate centrifugation tubes used by Diamond, or Diekmann and Graas, respectively, to arrive at the claimed device. The function of the Liotta device is to provide a one-step, one piece, device usable for both contact of test materials with sample and positive or negative result detection. Separation of the reaction layers from the colorimetric detection layer is not contemplated and it would defeat the simplification they were

striving for in Liotta. The Examiner provides no reason why such a separation would be undertaken by one of ordinary skill in the art.

With respect to the claim requirement that the column have a discharge point which is proximate to the solid support contained in the sleeve, we note that the hybridization procedure taught by Diamond involves an incubation time of between 15 minutes and 2 hours for the test material and the DNA in the sample to complete the reaction. See column 14, lines 30-43 of Diamond. A device with an open discharge end as claimed herein would not be conducive to such reaction times. The separations mentioned by Diamond at column 14, lines 53-63 do not use a flow-through column with both a discharge end and an open end as required by the claims at issue. Diamond also contemplates determining displaced labeled polynucleotide without any separation of the solid and liquid phases. See column 15, lines 13-36 of Diamond. The evidence presented to date does not establish the obviousness of this difference in tube design between the claimed device and the reaction tube of Diamond. We note that the devices taught by Diekmann and Graas have such discharge points in the columns but such are not proximate to a solid support, which provision has been discussed, supra.

In addition, the claim limitations with respect to the complex contained on the column support are neither exhibited nor suggested by the cited references. Claim 70, and thus all of the claims require as the third element:

> a specific antibody binder covalently immobilized on said first solid phase support to which an analyte label is pre-reacted to saturate substantially all binding sites on said binder to form a first solid phase specific antibody binder-analyte label complex ....

Diamond is not drawn to antibody-analyte complexes. To the extent that any analogy could be drawn, "substantially all of the binding sites" of the target DNA of Diamond are not saturated. Referring to Figures 1A and 1B of Diamond one can see this aspect. The rejection suggests that the TBR (target binding region) of the immobilized probe (P) of Diamond is analogous to the antibody, and the labeled polynucleotide (L) is analogous to the "analyte label." However, saturation of all of the binding sites of the TBR does not take place in Diamond. In fact saturation of all of the "binding sites" of the probe would disable the DNA hybridization required by Diamond. The IBR (initial binding region) of the TBR is not bound to any DNA prior to the addition of the sample of DNA, while the LBR (label binding region) is bound to the labeled polynucleotide (L). See Figure 1A of Diamond. The "binding sites" of the IBR must remain

unbound in order for sample DNA (G) to hybridize to it. See Figure 1B of Diamond. The DNA hybridization assay would not operate if all of
the target region of the probe (TBR) was "saturated" by being bound to labeled polynucleotide (L).

Similarly, the device taught by Liotta could not operate if substantially all of the antibody binding sites are saturated prior to addition of the sample. The device of Liotta requires the binding sites to be freely available. Saturation will occur either with the binding partner in the sample or the binding partner in the immobilized phase if the sample is free of the binding partner. See column 3, lines 17-25 in conjunction with Figures 5 and 6 of Liotta. As depicted in those figures the antibody is labeled. If there is antigen in the sample it will occupy the binding sites of the labeled antibody. By so occupying the binding sites the antibody will not become trapped by binding to the immobilized antigen in Zone 1, thus it will pass on to Zone 2 and the presence of the label will be detected by a visible color reaction in Zone 2. When the sample is free of antigen the labeled antibody will move into the region containing the immobilized antigen where it will be trapped via binding to

the immobilized antigen, thus it doesn't move on to Zone 2 and no color reaction occurs. If the binding sites of the labeled antibody were saturated prior to the addition of sample it would always move through to Zone 2 whether there is antigen in the sample or not. This would defeat the operation of the assay.

It has been held that it is not obvious to modify a prior art device in a manner which would lead to an inoperative construction. In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Since neither Diamond not Liotta could function as they were intended with substantially all binding sites saturated, one cannot conclude that such a modification of these devices would be obvious.

The generic references in Diekmann and Graas do not describe diagnostic materials with a specificity to suggest saturation of all binding sites of an immobilized material.

Due to the failure of the applied art to teach or suggest all of the elements of the claimed device, the Examiner has not met the burden of establishing a prima facie case under 35 U.S.C. § 103. Finding no prima facie case of obviousness in any of the three rejections, we reverse each of them.

The Examiner's decision refusing to allow claims 70-90 under 35 U.S.C. § 103 is reversed.

REVERSED

RICHARD E. SCHAFER, Vice-Chief Administrative Patent Judge	)
TEDDY S. GRON Administrative Patent Judge	) BOARD OF PATENT APPEALS AND INTERFERENCES
ELIZABETH C. WEIMAR Administrative Patent Judge	)

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